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(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM PLC** [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ARMSTRONG, Sula, Anne** [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **BERGE, John, Michael** [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **BROWN, Pamela** [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **ELDER, John, Stephen** [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **FORREST, Andrew, Keith** [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **HAMPRECHT, Dieter, Wolfgang** [DE/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **JARVEST, Richard, Lewis** [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: **CONNELL, Anthony, Christopher**; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

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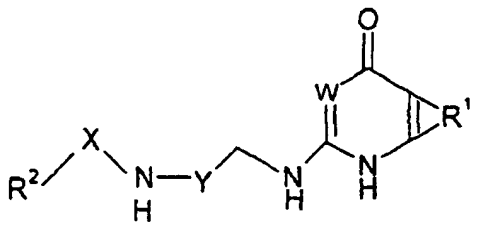
(54) Title: 2-NH-PYRIDONES AND PYRIMIDONES AS MRS INHIBITORS



(I)

(57) Abstract: Compounds of formula (I) in which: W is CH and R^1 is the residue of a 5 or 6-membered heteroaryl ring, or W is N and R^1 is the residue of an 5 or 6-membered heteroaryl ring or an aryl ring, which heteroaryl or aryl ring is optionally substituted with from 1 to 3 substituents selected from halo, cyano, hydroxy, (C_{1-6})alkyl(optionally substituted by halo, hydroxy, amino, mono to perfluoro(C_{1-3})alkyl, carboxy or (C_{1-6})alkoxycarbonyl), (C_{3-7})cycloalkyl, $C_{(1-6)}$alkoxy, amino, mono- or di-(C_{1-6})alkylamino, acylamino, carboxy, (C_{1-6})alkoxycarbonyl, carboxy(C_{1-6})alkyloxy, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, sulphamoyl, mono- and di-(C_{1-6})alkylsulphamoyl, carbamoyl, mono- and di-(C_{1-6})alkylcarbamoyl, and heterocyclyl; R^2 is an optionally substituted aryl or an optionally substituted heteroaryl ring; X is CH_2 or CHR^3 in which R^3 is $C_{(1-6)}$akyl or R^3 may be linked to the ortho position of an aryl or heteroaryl ring of R^2 to form a 5 to 7 membered ring optionally including oxygen or nitrogen as a ring atom; Y is $C_{(1-3)}$alkylene or $C_{(4-6)}$cycloalkylene; including tautomeric forms of the pyrimidone ring (when W is N); and salts thereof, preferably pharmaceutically acceptable salts thereof, are inhibitors of the bacterial enzyme S aureus methionyl t-RNA synthetase (MRS) and are of use in treating bacterial infections.

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2-NH-PYRIDONES AND PYRIMIDONES AS MRS INHIBITORS

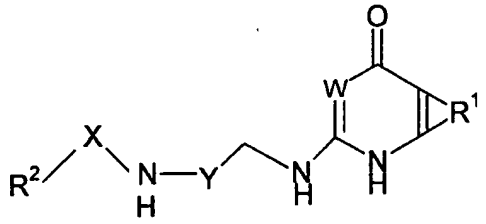
The present invention relates to novel 2-NH-pyridones and pyrimidones which are inhibitors of methionyl t-RNA synthetase (MRS), processes for their preparation and their use in therapy as anti-bacterial agents.

t-RNA synthetases are involved in protein biosynthesis so that inhibition thereof may be expected to lead to a cessation of cell growth. Thus, for instance, the compound mupirocin, produced by the organism *Pseudomonas fluorescens*, is an anti-bacterial agent and is used as the active ingredient in the product Bactroban, marketed by SmithKline Beecham. Mupirocin has been shown to be an inhibitor of the isoleucyl t-RNA synthetase. Each t-RNA synthetase represents a separate target for drug discovery. t-RNA synthetase inhibitors which are selective for bacterial cells over mammalian cells are of considerable therapeutic interest as they have the potential to be used as anti-bacterial agents.

The sequence of the t-RNA synthetase genes in organisms such as *S aureus* have recently been determined, see for instance European Patent application no 97300317.1 (SmithKline Beecham, *S aureus* MRS), thereby assisting the process of identifying inhibitors.

WO 99/ and WO 00/21949 (SmithKline Beecham, published after the priority date of the present application) describe a class of 2-(NH- or O-substituted) quinolones which are potent inhibitors of methionyl t-RNA synthetase

We have now found a further class of compounds which are potent inhibitors of methionyl t-RNA synthetase viz 2-NH - substituted (hetero)aryl fused pyridones and pyrimidones. Accordingly, the present invention provides a compound of the formula (I):



(I)

in which:

W is CH and R^1 is the residue of a 5 or 6-membered heteroaryl ring, or W is N and R^1 is the residue of an 5 or 6-membered heteroaryl ring or an aryl ring, which heteroaryl or aryl ring is optionally substituted with from 1 to 3 substituents selected from halo, cyano, hydroxy, (C_{1-6})alkyl (optionally substituted by halo, hydroxy, amino, mono to perfluoro(C_{1-3})alkyl, carboxy or (C_{1-6})alkoxycarbonyl), (C_{3-7})cycloalkyl, $C_{(1-6)}$alkoxy, amino, mono- or di-(C_{1-6})alkylamino, acylamino, carboxy, (C_{1-6})alkoxycarbonyl, carboxy(C_{1-6})alkyloxy, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, sulphamoyl, mono- and di-(C_{1-6})alkylsulphamoyl, carbamoyl, mono- and di-(C_{1-6})alkylcarbamoyl, and heterocyclyl;

R^2 is an optionally substituted aryl or an optionally substituted heteroaryl ring;X is CH_2 or CHR^3 in which R^3 is $C_{(1-6)}$alkyl or R^3 may be linked to the ortho position of an aryl or heteroaryl ring of R^2 to form a 5 to 7 membered ring optionally including oxygen or nitrogen as a ring atom;

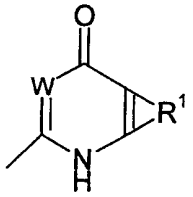
Y is $C_{(1-3)}$alkylene or $C_{(4-6)}$cycloalkylene;

including tautomeric forms of the pyrimidone ring (when W is N); and salts thereof, preferably pharmaceutically acceptable salts thereof.

Compounds of formula (I) are inhibitors of *S aureus* methionyl tRNA synthetase.

Representative examples of R^1 when the residue of a heteroaryl ring include rings in which the heteroatom is sulphur, for instance thieno, or nitrogen, for instance pyrido, pyrimido and pyrazolo. Representative examples of R^1 when the residue of an aryl ring include phenyl. Representative substituents therefor include halogen, for instance chloro or bromo.

Representative examples of the moiety:



include:

W = N and R^1 is the residue of an aryl ring: 1*H*-quinazolin-4-one;

W = CH and R^1 is the residue of a heteroaryl ring: 7*H*-thieno[2,3-*b*]pyridin-4-one, 4*H*-thieno[3,2-*b*]pyridin-7-one, 4*H*-thieno[3,4-*b*]pyridin-7-one, 1*H*-1,8-naphthyridin-4-one;

W = N and R^1 is the residue of a heteroaryl ring: 1*H*-thieno[3,2-*d*]pyrimidin-4-one, 1*H*-thieno[2,3-*d*]pyrimidin-4-one, 1*H*-thieno[3,4-*d*]pyrimidin-4-one, 1*H*-pyrido[3,2-*d*]pyrimidin-4-one; 1*H*-pyrimido[4,5-*d*]pyrimidin-4-one, and 1,7-dihydropyrazolo[3,4-*d*]pyrimidin-4-one.

Preferably, R^1 forms the residue of a thieno ring.

Representative examples of R^2 when aryl include phenyl and naphthyl, each of which may be optionally substituted with up to four substituents. Representative examples of such substituents include $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxy, $C_{(1-6)}$ alkylthio, heterocyclyl$C_{(1-6)}$ alkoxy , halo, cyano, amino, sulphamoyl, phenylcarbonyl, aryl, and benzyloxy. Preferably, the phenyl or naphthyl is substituted by two or three lipophilic substituents such as chloro, bromo, iodo, methyl, methoxy, allyloxy, phenethyloxy, morpholinopropoxy or trifluoromethyl.

Representative examples of R^2 when heteroaryl include pyrrolyl, thienyl, furanyl, pyridyl, quinolinyl, benzofuranyl, and indolyl, each of which may be optionally substituted with up to three substituents. Preferably, the heteroaryl ring is substituted by two or three lipophilic substituents such as chloro, bromo, iodo, methyl, methoxy or trifluoromethyl. Representative examples of such substituents include halo.

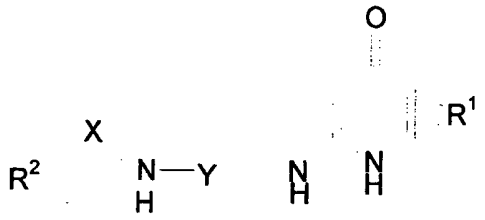
Preferred examples of aryl and heteroaryl groups for R^2 include phenyl, thienyl and indolyl.

Representative examples of X include CH_2 or forming, with R^2, a 5 to 7-membered ring optionally containing oxygen or nitrogen fused to an aryl or heteroaryl ring.

Representative examples of R^2X include benzyl, chroman-4-yl, 1,2,3,4-tetrahydroquinolin-4-yl, indol-2-ylmethyl, indol-7-ylmethyl, and thien-2-ylmethyl in which the aryl/heteroaryl ring may be optionally substituted.

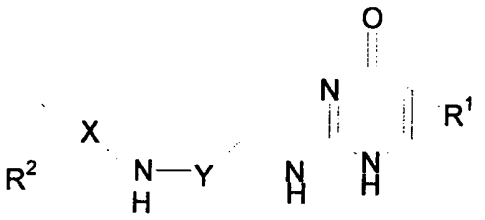
Representative examples of Y include a C_2 alkylene chain or a 1,2-cyclopentylene group.

It will be appreciated that within the compounds of formula (I) there exists a first set of pyridone compounds which W is CH:



(IA)

and a second set of pyrimidone compounds in which W is N:



(IB)

and in which R^1, R^2, X and Y are as hereinbefore defined.

Salts may be formed from inorganic and organic acids. Representative examples of suitable inorganic and organic acids from which pharmaceutically acceptable salts of compounds of formula (I) may be formed include maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

When used herein, the term "alkyl" and similar terms such as "alkoxy" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

Preferred substituents for an alkyl group include, for example, and unless otherwise defined, halogen, cyano, azido, nitro, carboxy, (C_{1-6})alkoxycarbonyl, carbamoyl, mono- or di-(C_{1-6})alkylcarbamoyl, sulpho, sulphamoyl, mono- or di-(C_{1-6})alkylsulphamoyl, amino, mono- or di-(C_{1-6})alkylamino, acylamino, ureido, (C_{1-6})alkoxycarbonylamino, 2,2,2-trichloroethoxycarbonylamino, aryl, heterocyclyl, hydroxy, (C_{1-6})alkoxy, acyloxy, oxo, acyl, 2-thienoyl, (C_{1-6})alkylthio, (C_{1-6})alkylsulphinyl, (C_{1-6})alkylsulphonyl, hydroxyimino, (C_{1-6})alkoxyimino, hydrazino, hydrazono, benzohydroximoyl, guanidino, amidino and iminoalkylamino.

When used herein, the term "aryl" includes, unless otherwise defined, phenyl or naphthyl optionally substituted with up to five, preferably up to three substituents.

When substituted, an aryl group may have up to three substituents. Preferred substituents for an aryl group include, for example, and unless otherwise defined, halogen, cyano, (C_1-6)alkyl, mono to perfluoro(C_1-3)alkyl, (C_3-7)cycloalkyl, (C_2-6)alkenyl, (C_1-6)alkoxy, (C_2-6)alkenoxy, aryl$C_{(1-6)}$alkoxy, halo(C_1-6)alkyl, hydroxy, amino, mono- or di-(C_1-6)alkylamino, acylamino, nitro, carboxy, (C_1-6)alkoxycarbonyl, (C_1-6)alkenyloxycarbonyl, (C_1-6)alkoxycarbonyl(C_1-6)alkyl, carboxy(C_1-6)alkyl, (C_1-6)alkylcarbonyloxy, carboxy(C_1-6)alkyloxy, (C_1-6)alkoxycarbonyl(C_1-6)alkoxy, (C_1-6)alkylthio, (C_1-6)alkylsulphinyl, (C_1-6)alkylsulphonyl, sulphamoyl, mono- and di-(C_1-6)-alkylsulphamoyl, carbamoyl, mono- and di-(C_1-6)alkylcarbamoyl, and heterocyclyl.

When used herein, the term "heteroaryl" includes single or fused rings comprising up to four hetero-atoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted with up to three substituents. Preferably the heteroaryl ring comprises from 4 to 7, preferably 5 to 6, ring atoms. A fused heteroaryl ring system may include carbocyclic rings and need only include one heterocyclic ring.

When used herein, the term "heterocyclyl" includes aromatic and non-aromatic single or fused rings comprising up to four hetero-atoms in the ring selected from oxygen, nitrogen and sulphur and optionally substituted with up to three substituents. Suitably the heterocyclic ring comprises from 4 to 7, preferably 5 to 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need only include one heterocyclic ring.

When substituted, a heteroaryl or a heterocyclyl group may have up to three substituents. Preferred such substituents include those previously mentioned for an aryl group as well as oxo.

When used herein, the terms "halogen" and "halo" include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

The compounds according to the invention are suitably provided in substantially pure form, for example at least 50% pure, suitably at least 60% pure, advantageously at least 75% pure, preferably at least 85% pure, more preferably at least 95% pure, especially at least 98% pure, all percentages being calculated as

weight/weight. An impure or less pure form of a compound according to the invention may, for example, be used in the preparation of a more pure form of the same compound or of a related compound (for example a corresponding derivative) suitable for pharmaceutical use.

Preferred compounds of formula (I) include:

2-[3-(3-Bromo-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one;

2 -[3-(3-Bromo-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;

2-[3-(3-Chloro-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one;

2 -[3-(3-Chloro-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;

2 -[3 -(3-Chloro-5-methyl-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;

2-[3-(6-Chloro-8-iodochroman-4-ylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;

2-[3-(6,8-Dibromochroman-4-ylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;

2-[3-(6-Bromo-8-chloro-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-quinazolin-4-one;

2-[3-(6,8-Dibromo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]- 1*H*-thieno[3,2-*d*]pyrimidin-4-one;

2-[3-(6,8-Dibromo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-quinazolin-4-one;

2-[3-(4,6-Dichloro-1*H*-indol-2-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one;

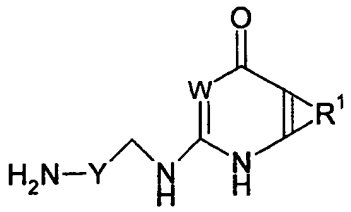
2-[3-(4,6-Dichloro-1*H*-indol-2-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;

2-{3-[3,5-Dibromo-2-(3-morpholinopropoxy)benzylamino]-prop-1-ylamino}-1*H*-quinazolin-4-one;

2-{3-[4,6-Dichloro-1-(2-hydroxyethyl)-1*H*-indol-2-ylmethylamino]prop-1-ylamino}-1*H*-thieno[3,2-d]pyrimidin-4-one; and

2-[3-(2-Ethoxy-5-iodo-3-methylbenzylamino)prop-1-ylamino]-1*H*-quinazolin-4-one.

A compound of formula (I) may be prepared by reacting a compound of formula (II):



(II)

in which R^1 , W and Y are as hereinbefore defined;
with either:

(a) for a compound of formula (I) in which X is CH_2, an aldehyde of formula (III):

$$R^2CHO \quad \text{(III)}$$

in which R^2 is as hereinbefore defined,
under reductive alkylation conditions;

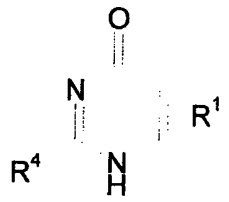
(b) for a compound of formula (I) in which X is CH_2 substituted by $C_{(1-6)}$ alkyl or in which R^2 and X are linked by a 5-7-membered ring opt. cont. oxygen or nitrogen, a ketone of formula (IV):

$$R^2R^3CO \quad \text{(IV)}$$

in which R^2 and R^3 are as hereinbefore defined,
under reductive alkylation conditions.

Suitable reductive alkylating conditions are well known in the art and include for instance, the use of sodium triacetoxyborohydride in a solvent system such as DMF/acetic acid or sodium cyanoborohydride in methanol/acetic acid. Reductive alkylation with an aldehyde is typically carried out at room temperature for a period of 1 - 16 h. Reductive alkylation with a ketone is typically carried out in refluxing methanol for a period of 16 - 40 h.

A compound of formula (IB) may be prepared by reacting a compound of formula (V):



(V)

in which R^1 is as hereinbefore defined; and

R^4 is a leaving group such as halo, for instance chloro, or $C_{(1-6)}$ alkylthio;

with an amine of the formula (VI):

$$R^2XNHYCH_2NH_2$$

(VI)

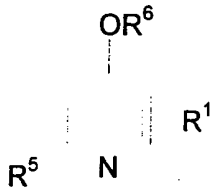
in which R^2, X and Y are as hereinbefore defined;

or an activated derivative thereof;

under nucleophilic displacement conditions.

Suitable conditions are well known in the art and include the use of a large excess of the compound of formula (VI) to drive the reaction to completion and heating at a temperature of 60 - 130 °C. Addition of a base may be advantageous in some cases, eg a tertiary base such as *N,N*-di(cyclohexyl)ethylamine.

A compound of formula (IA) may also be prepared by reacting a compound of formula (VII):



(VII)

in which R^1 is as hereinbefore defined;

R^5 is a leaving group such as halo, for instance chloro; and

R^6 is a $C_{(1-6)}$ alkyl, for instance methyl or ethyl, or an aryl$C_{(1-4)}$ alkyl group;

with an amine of the formula (VI), as hereinbefore defined;

or an activated derivative thereof;

under nucleophilic displacement conditions; to form an intermediate which is then converted into a compound of formula (IA) by acidic hydrolysis.

Suitable conditions are well known in the art and include the use of a large excess of the compound of formula (VI) to drive the reaction to completion and heating at a temperature of 60 - 130 °C. Addition of a base may be advantageous in some cases, eg a tertiary base such as *N,N*-di(cyclohexyl)ethylamine. Acid hydrolysis may be carried out with refluxing concentrated hydrochloric acid where R^6 is methyl or with trifluoroacetic acid at room temperature where R^6 is 4-methoxybenzyl.

A compound of formula (II) may be prepared by reacting a compound of formula (VII) with a compound of formula (VI) in which R^2 is hydrogen.

The compounds of this invention are active against both Gram negative and Gram positive organisms, including *Haemophilus*, for instance *H. influenzae* Q1; *Moraxella*, for instance *M. catarrhalis* 1502; *Streptococci*, for instance *S. pyogenes* CN10 and *S. pneumoniae* R6; *Staphylococci*, for instance *S. aureus* Oxford; *Escherichia*, for instance *E. Coli* DC0, and *Enterococci*, for instance *Ent. faecelis* I. In addition, compounds of this invention are active against *Staphylococci* organisms such as *S. aureus* and coagulase negative strains of *Staphylocci* such as *S. epidermidis* which are resistant (including multiply-resistant) to other anti-bacterial agents, for instance, β-lactam antibiotics such as, for example, methicillin; macrolides; aminoglycosides, and lincosamides. Compounds of the present invention are therefore useful in the treatment of MRSA, MRCNS and MRSE. Compounds of the present invention are also active against strains of *E. faecalis* including vancomycin resistant strains and therefore of use in treating infections associated with VRE organisms. Furthermore, compounds of the present invention are useful in the treatment of *Staphylococci* organisms which are resistant to mupirocin.

Bacterial infections which may be treated include respiratory tract infections, otitis, meningitis, endocarditis, skin and soft tissue infections in man, mastitis in cattle, and respiratory infections in animals such as pigs and cattle. Accordingly, in a further aspect, the present invention provides a method of treating bacterial infection in human or non-human animals, which method comprises administering a therapeutically effective amount of a compound of formula (I) as hereinbefore defined, to a human or non-human animal in need of such therapy.

The present invention provides a pharmaceutical composition comprising a compound of formula (I) together with a pharmaceutically acceptable carrier or excipient.

The present invention also provides a method of treating bacterial infections in animals, especially in humans and in domesticated mammals, which comprises administering a compound of formula (I), or a composition according to the invention, to a patient in need thereof.

The invention further provides the use of a compound of formula (I) in the preparation of a medicament composition for use in the treatment of bacterial infections.

The compounds and compositions according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The compounds and compositions according to the invention may be formulated for administration by any route, for example oral, topical or parenteral. The compositions may, for example, be made up in the form of tablets, capsules, powders, granules, lozenges, creams, syrups, or liquid preparations, for example solutions or suspensions, which may be formulated for oral use or in sterile form for parenteral administration by injection or infusion.

Tablets and capsules for oral administration may be in unit dosage form, and may contain conventional excipients including, for example, binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; and pharmaceutically acceptable wetting agents, for example sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or another suitable vehicle before use. Such liquid preparations may contain conventional additives, including, for example, suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate or acacia; non-aqueous vehicles (which may include edible

oils), for example almond oil, oily esters (for example glycerine), propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and, if desired, conventional flavouring and colour agents.

Compositions according to the invention intended for topical administration may, for example, be in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, impregnated dressings, and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.

Compositions according to the invention may be formulated as suppositories, which may contain conventional suppository bases, for example cocoa-butter or other glycerides.

Compositions according to the invention intended for parenteral administration may conveniently be in fluid unit dosage forms, which may be prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, may be either suspended or dissolved in the vehicle. In preparing solutions, the compound may be dissolved in water for injection and filter-sterilised before being filled into a suitable vial or ampoule, which is then sealed. Advantageously, conventional additives including, for example, local anaesthetics, preservatives, and buffering agents can be dissolved in the vehicle. In order to enhance the stability of the solution, the composition may be frozen after being filled into the vial, and the water removed under vacuum; the resulting dry lyophilized powder may then be sealed in the vial and a accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions may be prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound may instead be sterilised by exposure to ethylene oxide before being suspended in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in such suspensions in order to facilitate uniform distribution of the compound.

A compound or composition according to the invention may suitably be administered to the patient in an antibacterially effective amount.

A composition according to the invention may suitably contain from 0.1% by weight, preferably from 10 to 60% by weight, of a compound according to the invention (based on the total weight of the composition), depending on the method of administration.

The compounds according to the invention may suitably be administered to the patient at a daily dosage of from 1.0 to 50 mg/kg of body weight. For an adult human (of approximately 70 kg body weight), from 50 to 3000 mg, for example about 1500 mg, of a compound according to the invention may be administered daily. Suitably, the dosage for adult humans is from 5 to 20 mg/kg per day. Higher or lower dosages may, however, be used in accordance with normal clinical practice.

When the compositions according to the invention are presented in unit dosage form, each unit dose may suitably comprise from 25 to 1000 mg, preferable from 50 to 500 mg, of a compound according to the invention.

The following Examples illustrate the present invention.

General method for reductive amination To a suspension of the amine (0.2 mmol) (containing 0.5 mmol sodium acetate if the amine was present as the dihydrochloride) in methanol (2 ml) was added the aldehyde (0.2 mmol) in methanol (2 ml) and acetic acid (0.033 ml). After stirring under argon for 10 min, $NaCNBH_3$ (24 mg, 0.4 mmol) in MeOH (1 ml) was added and the reaction stirred for 16 h. The reaction mixture was applied to a 2 g Varian Bond Elute SCX cartridge which was flushed with MeOH (8 ml). The cartridge was then eluted with 8 ml 0.2 M NH_3 in MeOH, and this eluate evaporated to dryness. The residue was purified by chromatography on silica gel eluting with 2-10% (9:1 MeOH/20 M NH_3) in CH_2Cl_2 . Product-containing fractions were combined and evaporated under reduced pressure to give the product as a white solid. To convert this into the corresponding dihydrochloride, the solid was dissolved in 1.0 M HCl in methanol (0.4 ml) and the solution evaporated to dryness.
An alternative method using polymer-supported cyanoborohydride was also used. (Polystyrylmethyl)trimethylammonium cyanoborohydride (Novobiochem) (3.64 mmol/g, 100 mg) was used in place of sodium cynoborohydride. The reaction was worked up by filtration, evaporation. followed by chromatography on silica gel as described above.

General method for alkylation of phenols To a solution of the phenol (1.2 mmol) and ethyl iodide (480 ul, 6 mmol) in dimethylformamide (2 ml) was added potassium carbonate (330 mg, 2.4 mmol). After stirring under argon at 65°C for 16 h the suspension was then diluted with diethyl ether, washed with water, dried ($MgSO_4$) and evaporated to afford the product.

Intermediate 1 - *N*-(3-Aminoprop-1-yl)-3,4-dichlorobenzylamine - To 1,3-diaminopropane (42 ml) in dry THF (200 ml) at 60 °C was added dropwise a solution of 3,4-dichlorobenzylchloride (13.9 ml, 100 mmol) in 90 ml dry THF over 3 h. The mixture was kept at 60 °C for an additional 15 min and then kept at 25 °C for 3 days. The precipitate was removed by filtration and the mother liquor concentrated *in vacuo*. The residue was partitioned between water and t-butyl methyl ether (TBME). To the organic layer was added aq. HCl (2 M) and the mixture was filtered. The layers were separated and NaOH was added to the aqueous layer with stirring. The resulting mixture was extracted with TBME and the organic extract was dried (Na_2CO_3), filtered, and the solvent evaporated to give the **title compound** as a slightly cloudy oil, (18.2 g, 78%). δ_H ($CDCl_3$) 1.20 (br, s, *ca.* 3H), 1.58-1.71 (m, 2H), 2.67 (t, J = 6.9, 2H), 2.78 (t, J = 6.8, 2H), 3.74 (s, 2H), 7.15 (dd, J = 8.2, 2.0, 1H), 7.37 (d, J = 8.2, 1H), 7.43 (d, J = 1.9, 1H); MS (ES^+) 233 (MH^+, 13%), 159 (100).

Intermediate 2: 2-(3-Aminopropylamino)-1*H*-quinazolin-4-one
2-(Methylsulfanyl)-1*H*-quinazolin-4-one (20 g; Chern *et al.*, *Tetrahedron Asymm.* **1996,** *7*, 1641-1648) and 1,3-diaminopropane (104 ml) were heated in a sealed vessel to 140 °C for 48 h. After cooling, a yellow crystalline solid was filtered off. The remaining reaction mixture was concentrated *in vacuo*, triturated with methanol, and purified by column chromatography. The crystals and the material obtained from chromatography were combined to yield the **title compound**: (12 g, 53%). δ_H (d_6-DMSO) 1.63 (m, 2H), 2.64 (m, 2H), 3.39 (m, 2H), 5.10 (v. br., 3H), 6.87 (br, *ca.*1H), 7.06 (m, 1H), 7.21 (m, 1H), 7.52 (m, 1H), 7.87 (m, 1H).

Intermediate 3: 2-(3-Aminopropylamino)-1*H*-thieno[3,2-*d*]pyrimidin-4-one
a) Potassium 1*H*-thieno[3,2-*d*]pyrimidin-4-one-2-thiolate - 3-(3-Benzoylthioureido)-2-thiophenecarboxylic acid methyl ester (75 g; Gutschow, *J. Het. Chem.* **1996**, *33*, 355-360) was added to a solution of KOH (25 g) in ethanol (1 l) and heated to reflux for 2.5 hours. A lemon coloured solid was filtered off to yield the **title compound** of about 85% purity which was used without further purification in the next step: (46 g). δ_H (d_6-DMSO) 6.87 (m, 1H), 7.22 (m, 1H), 10.35 (br, 1H) plus benzoate impurity.
b) 2-Methylsulfanyl-1*H*-thieno[3,2-*d*]pyrimidin-4-one - Potassium 1*H*-thieno[3,2-*d*]pyrimidin-4-one-2-thiolate (46 g) of about 85% purity was added to water (1 l). Methyl iodide (13 ml) was added and the mixture was stirred for 3 h. A white precipitate was filtered off and dried to yield the **title compound** as an off-white solid: (30 g, 82%). δ_H (d_6-DMSO) 2.55 (s, 3H), 7.31 (d, *J*=5.2 Hz, 1H), 8.13 (d, *J*=5.2 Hz, 1H), 12.78 (br, 1H).
c) 2-(3-Aminopropylamino)-1*H*-thieno[3,2-*d*]pyrimidin-4-one - 2-Methylsulfanyl-1*H*-thieno[3,2-*d*]pyrimidin-4-one (20 g) was treated in the same way as described for **Intermediate 2** to yield the **title compound**: (8.0 g, 35%). δ_H (d_6-DMSO) 1.96 (m, 2H), 2.96 (m, 2H), 3.69 (m, 2H), 5.16 (br, ca. 4H under H_2O peak), 7.54 (d, *J*=5, 1H), 8.28 (d, *J*=5, 1H).

Where the dihydrochloride salts of **intermediates 2 or 3** were used, these were obtained quantitatively from the free amines by treatment with concentrated aqueous HCl in methanol and evaporation.

Example 1 - 6-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-7*H*-thieno[2,3-*b*]pyridin-4-one dihydrochloride
a) *N*-(3,5-Dibromobenzyl)propane-1,3-diamine - 3,5-Dibromobenzyl bromide (9.96 g, 30.2 mmol) was dissolved in THF (70 ml) and added dropwise over 90 minutes to a solution of propane-1,3-diamine (12.6 ml, 151 mmol) in THF (50 ml) at 60°C. The solution was stirred under argon for a further 30 min, filtered and the filtrate concentrated. The residues were partitioned between *tert*-butylmethylether

and H_2O, the organic layer separated and aqueous HCl (1 M) added. The aqueous layer was separated, filtered and basified to pH 13 (NaOH pellets). The solution was extracted with $CHCl_3$, dried (K_2CO_3), and evaporated under reduced pressure to yield the **title compound** as a yellow oil (6.21 g, 19 mmol): δ_H ($CDCl_3$) 1.36 (br, s, 3H + H_2O), 1.65 (m, 2H), 2.67 (t, *J* 6.7, 2H), 2.79 (t, *J* 6.7, 2H), 3.74 (s, 2H), 7.42 (d, *J* 1.6, 2H), 7.54 (t, *J* 1.6, 1H,); MS (ES+) 323 (100%, $[M+H]^+$), 306 (75), 249 (100).

b) 6-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-4-methoxythieno[2,3-*b*]pyridine - 2-Chloro-4-methoxythieno[2,3-*b*]pyridine (*J. Chem. Res. Miniprint* **1985**, 2501; 275 mg, 1.38 mmol) was heated with *N*-(3,5-dibromobenzyl)propane-1,3-diamine, **Example 1a**, (1.33 g, 4.14 mmol) in a Wheaton reactivial at 130°C for 40 h. The resulting oil was purified by flash chromatography on silica gel eluting with 5-10% [10:1 MeOH/conc. NH_3(aq.)] in CH_2Cl_2 to yield the **title compound** as a white solid (70 mg, 0.144 mmol); δ_H (CD_3OD) 1.83 (m, 2H), 2.66 (t, *J* 7.0, 2H), 3.44 (t, *J* 6.7, 2H), 3.69 (s, 2H), 3.91 (s, 3H), 5.98 (s, 1H), 6.94 (d, *J* 5.9, 1H), 7.11 (d, *J* 5.9, 1H), 7.48 (d, *J* 1.7, 2H), 7.58 (t, *J* 1.7, 1H); MS (ES+) 486 (50%, $[M+H]^+$), 186 (100).

c) 6-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-7*H*-thieno[2,3-*b*]pyridin-4-one dihydrochloride - To the compound of **Example 1b** (70 mg, 0.144 mmol) in 1,4-dioxane (2 ml) was added concentrated hydrochloric acid (8 ml). The mixture was refluxed at 110 °C for 32 h. The mixture was filtered and evaporated to low volume under reduced pressure to leave an off-white residue which was purified by flash chromatography on silica gel eluting with 5-10-25% [10:1 MeOH/conc. NH_3(aq.)]. The isolated material was dissolved in MeOH and concentrated hydrochloric acid was added. The excess solvents were evaporated under reduced pressure to yield the **title compound**, isolated as the dihydrochloride salt, as a white solid (5 mg, 0.009 mmol); δ_H (CD_3OD) 1.78 (m, 2H), 2.70 (t, *J* 7.0, 2H), 3.30 (t, *J* 6.6, 2H), 3.76 (s, 2H, $ArC\underline{H}_2N$), 5.39 (s, 1H, $\underline{H}CCO$), 6.85 (d, 1H, *J* 5.7, thiophene), 7.09 (d, 1H, *J* 5.7, thiophene), 7.45 (d, 2H, *J* 1.7, $BrCC\underline{H}CCH_2$), 7.56 (t, 1H, *J* 1.7, $BrCC\underline{H}CBr$); MS (ES+) 472 (100%).

Example 2 - 5-[3-(3,4-Dichlorobenzylamino)prop-1-ylamino]-4*H*-thieno[3,2-*b*]pyridin-7-one dihydrochloride

a) 5-Chloro-7-methoxythieno[3,2-*b*]pyridine - 15-Crown-5 (1.46 ml, 7.35 mmol) was added to a solution of NaOMe (400 mg, 7.35 mmol) in THF (10 ml) and stirred for 15 minutes. 5,7-Dichlorothieno[3,2-*b*]pyridine (*J. Chem. Res. Miniprint* **1980**, 0113; 1g , 4.9 mmol) was added, resulting in a deep purple suspension which was stirred under Ar for 90 minutes. The reaction mixture was partitioned between NH_4Cl (aq) and *tert*-butylmethylether, the layers separated, the organic layer washed with brine, and concentrated under reduced pressure.

The residue was purified by flash chromatography on silica gel eluting with 4:1-3:1 [hexanes/ethyl acetate] to give the **title compound** as an off-white solid (790 mg, 3.96 mmol); δ_H ($CDCl_3$) 4.05 (s, 3H), 6.74 (s, 1H), 7.44 (d, *J* 5.4, 1H), 7.70 (d, *J* 5.4, 1H); MS (ES+) 200 (75%, $[M+H]^+$), 164 (100), 149 (63).

b) 5-[3-(3,4-Dichlorobenzylamino)prop-1-ylamino]-7-methoxythieno[3,2-*b*]pyridine - A mixture of 5-chloro-7-methoxythieno[3,2-*b*]pyridine, **Example 2a** (0.40 g) and *N*-(3-aminoprop-1-yl)-3,4-dichlorobenzylamine (*ca.* 0.59 ml) was kept at 85 °C for 15 h and then at 125 °C for 4 h. Column chromatography (silica gel, MeOH : NH_3 : CH_2Cl_2 10 : 1 : 100 → 30 : 3 : 200) separated residual 5-chloro-7-methoxythieno[3,2-*b*]pyridine (0.17 g) from material containing the title compound which was again submitted to column chromatography (silica gel, MeOH : NH_3 : CH_2Cl_2 10 : 1 : 100) to give the **title compound** (17 mg) as a yellow film: δ ($CDCl_3$) 1.71 (br, s, 1H, NH), 1.78-1.90 (m, 2H, $CH_2CH_2CH_2$), 2.76 (t, *J* 6.4, 2 H, CH_2NHCH_2), 3.47-3.55 (m, 2H, CH_2N), 3.74 (s, 2H, $ArCH_2$), 3.95 (s, 3H, OCH_3) 4.97 (br, s, 1 H, NH), 5.83 (s, 1 H, CHCO), 7.12-7.17 (m, 2H, 2Ar-H), 7.36 (d, *J* 8.2, 1 H, Ar-H), 7.44 (d, *J* 1.9, 1H, ArH), 7.50 (d, *J* 5.4, 1 H, Ar-H); *m/z* (ESI) 396 (MH^+, 20%), 221 (100%).

c) 5-[3-(3,4-Dichlorobenzylamino)prop-1-ylamino]-4*H*-thieno[3,2-*b*]pyridin-7-one dihydrochloride - The compound of **Example 2b** (17 mg) in dioxane (1 ml) and concentrated aq. HCl (5 ml) was heated at reflux for 48 h. Volatiles were evaporated *in vacuo* and the residue was triturated with $CHCl_3$ and filtered to give the **title compound** as an off-white solid (18 mg): δ_H (CD_3OD) 2.08-2.25 (m, 2H, $CH_2CH_2CH_2$,), 3.21-3.31 (m, 2 H, CH_2NHCH_2), 3.54-3.63 (m, 2H, CH_2N), 4.29 (s, 2H, $ArCH_2$), 6.27 (s, 1 H, CHCO), 7.45-7.54 (m, 2H, 2Ar-H), 7.66 (d, *J* n.d., 1 H, Ar-H), 7.80 (d, *J* n.d., 1 H, Ar-H), 8.10 (d, 1H, *J* n.d., ArH); *m/z* (ESI) 382 (MH^+, 68%), 207 (100%).

Example 3 - 5-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-4*H*-thieno[3,2-*b*]pyridin-7-one dihydrochloride

a) 5-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-7-methoxythieno[3,2-*b*]pyridine - 5-Chloro-7-methoxythieno[3,2-*b*]pyridine, **Example 2a**, (345 mg, 1.73 mmol) was heated *N*-(3,5-dibromobenzyl)propane-1,3-diamine, **Example 1a**, (1.67 g, 5.19 mmol) in a Wheaton reactivial at 130 °C for 40 h. The resulting oil was purified by flash chromatography on silica gel eluting with 5-10% [10:1 MeOH/conc. NH_3(aq.)] in CH_2Cl_2 to yield the **title compound** as a white solid (40 mg, 0.08 mmol); δ_H (CD_3OD) 1.86 (m, 2H), 2.69 (t, *J* 7.0, 2H), 3.45 (t, *J* 6.8, 2H), 3.72 (s, 2H), 3.96 (s, 3H), 6.06 (s, 1H), 7.11 (d, *J* 5.3, 1H), 7.49-7.53 (m, 2H), 7.59-7.61 (m, 2H); MS (ES+) 486 (100%, $[M+H]^+$).

b) 5-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-4*H*-thieno[3,2-*b*]pyridin-7-one dihydrochloride - To the compound of **Example 3a** (40 mg, 0.08 mmol)

in 1,4-dioxane (2 ml) was added concentrated hydrochloric acid (8 ml). The mixture was refluxed at 110 °C for 32 h. The mixture was filtered and evaporated under reduced pressure to leave an off-white residue which was purified by flash chromatography on silica gel eluting with 5-10-25% [10:1 MeOH/conc. NH_3(aq.)] in CH_2Cl_2. The isolated material was dissolved in MeOH and concentrated hydrochloric acid was added. Solvents were evaporated under reduced pressure to yield the **title compound**, isolated as the dihydrochloride salt, as a white solid (4 mg, 0.007 mmol); δ_H (CD_3OD) 2.18 (m, 2H), 3.28 (m, 2H), 3.60 (t, *J* 6.6, 2H), 4.30 (s, 2H, $ArCH_2N$), 6.27 (s, 1H, HCCO), 7.47 (d, *J* 5.4, 1H, thiophene), 7.77 (d, *J* 1.4, 2H, HCCCH2), 7.90 (t, *J* 1.4, 1H, BrCCHCBr), 8.08 (d, *J* 5.4, 1H, thiophene); MS (ES+) 472 (100%, $[M+H]^+$).

Example 4 - 2-[3-(3,4-Dichlorobenzylamino)prop-1-ylamino]-1*H*-1,8-naphthyridin-4-one dihydrochloride

a) 2-Chloro-4-methoxy-1,8-naphthyridine - To 2,4-dichloro-1,8-naphthyridine (*Berichte* **1927**, 60, 407; 0.43 g) was added NaOMe in MeOH (1 M, 4.3 ml) and the mixture was heated at reflux for 30 min. EtOAc (*ca.* 5 ml) was added and then removed *in vacuo* and this procedure was repeated. The resulting material was submitted to column chromatography (silica gel, EtOAc : hexanes 2 : 1 → 3 : 1 → EtOAc) to give 4-chloro-2-methoxy-1,8-naphthyridine (211 mg, colourless crystals) followed by the **title compound**: colourless crystals (117 mg), δ ($CDCl_3$) 4.09 (s, 3 H, OCH_3), 6.83 (s, 1 H, 3-H), 7.46 (dd, *J* 8.3, 4.3, 1 H, 6-H), 8.50 (dd, *J* n.d., 1H), 9.07 (dd, *J* n.d., 1 H); *m/z* (ESI) 217 (MNa^+, 5%), 195 (MH^+, 100%).

b) 2-[3-(3,4-Dichlorobenzylamino)prop-1-ylamino]-4-methoxy-1,8-naphthyridine - A mixture of 2-chloro-4-methoxy-1,8-naphthyridine, **Example 4a**, (0.11 g) and *N*-(3-aminoprop-1-yl)-3,4-dichlorobenzylamine (*ca.* 0.17 ml) in acetonitrile (1 ml) and *N,N*-diisopropylethylamine (1 ml) was kept at 85 °C for 4 h, then at 25 °C for 15 h, then again at 85 °C for 24 h. Volatiles were evaporated *in vacuo* and the residue submitted to column chromatography (silica gel, MeOH : NH_3 : CH_2Cl_2 10 : 1 : 100) to give the **title compound** (163 mg) as a slightly yellow oil: δ ($CDCl_3$) 1.79-1.91 (m, 3H, $CH_2CH_2CH_2$ + NH), 2.77 (t, *J* 6.3, 2 H, CH_2NHCH_2), 3.71 (t, *J* 6.2, 2H, CH_2N), 3.74 (s, 2H, $ArCH_2$), 5.76 (br, t, *J* n.d., 1 H, NH), 5.89 (s, 1 H, CHCO), 7.07 (dd, *J* 8.0, 4.5, 1H, Ar-H), 7.14 (dd, *J* n.d., 1H, Ar-H), 7.34 (d, *J* 8.2, 1 H, Ar-H), 7.44 (d, *J* 1.9, 1 H, Ar-H), 8.22 (dd, *J* n.d., 1H, ArH), 8.75 (dd, *J* n.d., 1 H, Ar-H); *m/z* (ESI) 391 (MH^+, 32%), 216 (100%).

c) 2-[3-(3,4-Dichlorobenzylamino)prop-1-ylamino]-1*H*-1,8-naphthyridin-4-one dihydrochloride - The compound of **Example 4b** (122 mg) in dioxane (2 ml) and concentrated aq. HCl (10 ml) was heated at reflux for 20 h. Volatiles were evaporated *in vacuo* and the residue was triturated with $CHCl_3$ and filtered to give

the **title compound** as a colourless solid (110 mg): δ_H (CD_3OD) 2.08-2.21 (m, 2H, $CH_2\underline{CH_2}CH_2$,), 3.17-3.25 (m, 2 H, $\underline{CH_2}NHCH_2$), 3.66-3.72 (m, 2H, $\underline{CH_2}N$), 4.26 (s, 2H, ArC<u>H</u>2), 6.40 (s, 1 H, C<u>H</u>CO), 7.45-7.55 (m, 2H, 2Ar-<u>H</u>), 7.62 (d, *J* 8.3, 1 H, Ar-<u>H</u>), 7.75 (d, *J* 2.0, 1 H, Ar-<u>H</u>), 8.61-8.83 (m, 2H, 2Ar<u>H</u>); *m/z* (ESI) 377 (MH^+, 28%), 202 (100%).

Example 5 - 2-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-1*H*-quinazolin-4-one

2-Methylthioquinazolin-4-one (*Tetrahedron: Asymmetry* **1996**, 7, 1641; 100 mg, 0.52 mmol) was heated with *N*-(3,5-dibromobenzyl)propane-1,3-diamine, **Example 1a,** (334 mg, 1 mmol) in a Wheaton reactivial at 85 °C for 24 h. The residue was purified by flash chromatography on silica gel eluting with 5-10-20% [10:1 MeOH/conc. NH_3(aq)] in CH_2Cl_2 to yield the product as an off-white solid (150 mg, 0.32 mmol); δH ($CDCl_3/CD_3OD$) 1.93 (m, 2H), 2.75 (t, *J* 6.7, 2H), 3.59 (t, *J* 6.5, 2H), 3.81 (s, 2H), 7.31 (m, 2H), 7.57 (s, 2H), 7.65 (m, 2H), 8.09 (m, 1H); MS (ES+) 467 (100%, $[M+H]^+$).

Example 6 – 2-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one dihydrochloride : *N*-(3,5-Dibromobenzyl)propane-1,3-diamine, **Example 5a,** (0.105 g, 0.33 mmol) and 2-ethylsulfanyl-1*H*-thieno[3,2-*d*]pyrimidin-4-one (*J. Med. Chem.,* **1995**, 38, 2763; 0.035 g, 0.165 mmol) were reacted together at 125°C for 24 h. The mixture was pre-absorbed onto silica and purified by flash chromatography, eluting with 0 – 10% '10% 0.880 ammonia in methanol' in dichloromethane, to give the free base as an off-white solid. This was suspended in methanol and treated with hydrochloric acid to give the **title compound** as an off-white powder (0.023 g, 26%); δ_H (CD_3OD) 2.2 – 2.35 (2H, m), 3.35 (2H, t), 3.77 (2H, t), 4.35 (2H, s), 7.48 (1H, br d), 7.85 – 7.95 (3H,m), and 8.25 (1H, d); LC/MS (ES+) 471, 473, 475 (50, 100, 50%, MH^+).

Example 7 - 6-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-1,7-dihydropyrazolo[3,4-*d*]pyrimidin-4-one

a) 6-Methylsulfanyl-1,7-dihydropyrazolo[3,4-*d*]pyrimidin-4-one: 4-Hydroxy-6-mercaptopyrazolo[3,4-*d*]pyrimidine (500 mg, 2.97 mmol) was added to a solution of potassium bicarbonate (300 mg, 3.0 mmol) and methyl iodide (0.2 ml, 3.0 mmol) in EtOH (15 ml) and stirred under Ar for 16 h. The reaction mixture was concentrated under reduced pressure, taken up in CH_2Cl_2:MeOH (10:1) and filtered, the filtrate evaporated under reduced pressure to give the **title compound** as an off-white solid (300 mg, 1.6 mmol); δ_H ($CDCl_3/CD_3OD$) 2.45 (s, 3H), 7.85 (s, 1H); MS(APCI+) 183 (100%, $[M+H]^+$); MS(APCI-) 181 (100%, $[M-H]^-$).

b) 6-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-1,7-dihydropyrazolo[3,4-*d*]pyrimidin-4-one: 6-Methylsulfanyl-1,7-dihydropyrazolo[3,4-*d*]pyrimidin-4-one, **Example 7a,** (100 mg, 0.55 mmol) was heated with *N*-(3,5-dibromobenzyl)propane-1,3-diamine, **Example 5a,** (350 mg,1.1 mmol) in a Wheaton reactivial to 90 °C for 24 h. The reaction mixture was purified by flash chromatography over silica gel eluting with 10-25-40% [10:1 MeOH/conc. NH_3(aq)] in CH_2Cl_2 to give the **title compound** as a white solid (20 mg, 0.04 mmol); δH ($CDCl_3$/CD_3OD) 1.80 (m, 2H), 2.66 (t, *J* 6.7, 2H), 3.45 (t, *J* 6.6, 2H), 3.72 (s, 2H), 7.42 (s, 2H), 7.57 (s, 1H), 7.91 (s, 1H); MS(ES+) 457 (100%, $[M+H]^+$).

Example 8 - 2-[3-(3-Bromo-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one

a) 5-Methoxyindoline-7-carbaldehyde. 1-(*tert*-Butoxycarbonyl)-5-methoxyindoline (*Heterocycles*, 1992, **34**, 1031; 1.75 g, 7.0 mmol) was dissolved in dry THF, treated with TMEDA (1.4 ml) and cooled to -78°C under an argon atmosphere. A solution of *s*-butyl lithium (1.3 M in cyclohexane, 5.18 ml) was added dropwise. After stirring at -78°C for 1 h, the solution was treated with dry DMF (1.08 ml, 14 mmol) and stirred for a further 0.5 h. The cooling bath was then removed and the solution allowed to reach room temperature over 1 h. The reaction mixture was quenched with 10% aqueous NH_4Cl and the product extracted into ethyl acetate. The extracts were combined, washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on Kieselgel 60 eluting with 0-20% ethyl acetate in hexane. Product-containing fractions were combined and evaporated to afford the **title compound** (510 mg); contaminated with 35% (by weight) of the corresponding N-Boc analogue; δ_H ($CDCl_3$, *inter alia*) 3.03 (2H, t, J =8.0 Hz, CH_2), 3.76 (2H, t, J =8.1 Hz, CH_2NH), 3.77 (3H, s, OMe), 6.42 (1H, br.s, NH), 6.73 (1H, d, J=0.8 Hz Ar-H), 6.90-6.92 (1H, m, Ar-H), 9.79 (1H, s, CHO).

b) 5-Methoxyindole-7-carbaldehyde. The product from **a)** (80 mg; containing 0.3 mmol 5-methoxyindoline-7-carbaldehyde) was dissolved in dichloromethane (10 ml) and treated with MnO_2 (344 mg, 4.0 mmol). The reaction mixture was stirred at room temperature for 16 h, filtered through Celite and the solvent removed in vacuo. The residue was chromatographed on Kieselgel 60 eluting with 0-20% ethyl acetate in hexane to afford the **title compound** as a pale yellow solid (23 mg, 44%), δ_H ($CDCl_3$) 3.91(3H, s, OMe), 6.56 (1H, dd, J= 2.2, 3.2 Hz, 3-H), 7.28 (1H, d, J=2.3 Hz, Ar-H), 7.33 (1H, t, J=2.6 Hz, 2-H), 7.46 (1H, m, Ar-H), 9.93 (1H, br.s., NH), 10.07 (1H, s, CHO).

c) 3-Bromo-5-methoxyindole-7-carbaldehyde. The product from **b)** (40 mg, 0.22 mmol) was dissolved in dichloromethane (5 ml), treated with N-

bromosuccinimide (40 mg), and the mixture stirred at room temperature for 16 h. The solution was then diluted with dichloromethane, washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on Kieselgel 60 eluting with 0-50% ethyl acetate in hexane. Product-containing fractions were combined and evaporated to afford the **title compound** as a pale pink solid (53 mg, 95%); δ_H ($CDCl_3$) 3.94 (3H, s, OMe), 7.34 (3H, s, 2-H, 4-H, 6-H), 9.93 (1H, br.s. NH), 10.06 (1H, s, CHO).

d) 2-[3-(3-Bromo-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one. The product from **c)** was coupled to **intermediate 2** on a 0.2 mmol scale using the **general method for reductive amination**, with polymer-supported $CNBH_3$ to give the **title compound** as a white solid (31 mg, 34%); *m/z* (CI^+) 456 (MH^+, 70%).

Example 9 - 2 -[3-(3-Bromo-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one

The product from **example 8c** was coupled to compound **intermediate 3** on a 0.15 mmol scale using the **general method for reductive amination**, to give the **title compound** as a white solid (15 mg, 22%); *m/z* (CI^+) 462 (MH^+, 100%).

Example 10 - 2-[3-(3-Chloro-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one a) 3-Chloro-5-methoxyindole-7-carbaldehyde. The product from **example 8b** (140 mg, 0.80 mmol) was dissolved in dichloromethane (10 ml), treated with N-chlorosuccinimide (105 mg), and the mixture stirred at room temperature for 16 h. The solution was then diluted with dichloromethane, washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on Kieselgel 60 eluting with 0-50% ethyl acetate in hexane. Product-containing fractions were combined and evaporated to afford the **title compound** as a pale pink solid (115 mg, 68%); δ_H ($CDCl_3$) 3.94 (3H, s, OMe), 7.28 (1H, d, *J* 2.5 Hz), 7.33 (1H, d, *J* 2.4 Hz), 7.39, (1H, d, *J* 2.4 Hz), 9.93 (1H, br.s. NH), 10.06 (1H, s, CHO).

b) 2-[3-(3-Chloro-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one. The product from **a)** was coupled to **intermediate 2** on a 0.15 mmol scale using the **general method for reductive amination**, with polymer-supported $CNBH_3$ to give the **title compound** as a white solid (31 mg, 50%); *m/z* (CI^+) 412 (MH^+, 80%).

Example 11 - 2 -[3-(3-Chloro-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one.

The product from **example 10a** was coupled to **intermediate 3** on a 0.2 mmol scale using the **general method for reductive amination**, with polymer-

supported cyanoborohydride, to give the **title compound** as a white solid (58 mg); *m/z* (CI^+) 418 (MH^+, 70%).

Example 12 - 2 -[3 -(3-Chloro-5-methyl-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one dihydrochloride

a) 5-Methylindole-7-carbaldehyde. 1-(*tert*-Butoxycarbonyl)-5-methylindoline (*J. Org Chem*, 1999, **64**, 3595; 2.9g 12.5 mmol) was converted to the 7-aldehyde as described for **example 8a**. A portion of this product (1.5 mmol) was converted to the corresponding indole as described for **example 8b**. The **title compound** was obtained as a yellow solid (167 mg, 64%); δ_H ($CDCl_3$) 2.53(3H, s, Me), 6.56 (1H, dd, J= 2.2, 3.0 Hz, 3-H), 7.30 (1H, t, J= 3.0 Hz, 3-H), 7.47 (1H, d, J=1.0 Hz, Ar-H), 7.47 (1H, d, J= 1.0 HzAr-H), 9.98 (1H, br.s., NH), 10.10 (1H, s, CHO).

b) 3-Chloro-5-methylindole-7-carbaldehyde . The product from **a)** (64 mg, 0.4 mmol) was converted to the title compound as described for **example 10a**, to give the **title compound** as a yellow solid (56 mg, 73%); δ_H ($CDCl_3$) 2.55 (3H, s, Me), 7.25 (1H, t, J= 3.2 Hz, 3-H), 7.45(1H, s, Ar-H), 7.72 (1H, s, Ar-H), 9.87 (1H, br.s., NH), 10.10 (1H, s, CHO).

c) 2 -[3 -(3-Chloro-5-methyl-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one dihydrochloride. The product from **b** was coupled to **intermediate 3** on a 0.15 mmol scale using the **general method for reductive amination**, with polymer-supported cyanoborohydride, followed by conversion to the correspoding dihydrochloride to give the **title compound** as a white solid (28 mg, 47%); *m/z* (CI^+) 402 (MH^+, 70%).

Example 13 - 2-[3-(3,5-Dibromo-2-ethoxybenzylamino)prop-1-ylamino]-1*H*-pyrido[3,2-*d*]pyrimidin-4-one dihydrochloride

a) 3-(3-Benzoylthioureido)pyridine-2-carboxylic acid ethyl ester. 3-Aminopyridine-2-carboxylic acid ethyl ester (1.3 g; Oakes *et al.*, *J. Chem. Soc.* **1956**, 1045) was dissolved in acetone (50 ml) and benzoyl isothiocyanate (2.2 ml) added. The solution was heated to reflux for 1 h and allowed to cool. The solution was concentrated *in vacuo* and a yellow precipitate was obtained on adding methanol to the resultant oil. This solid was filtered off to yield the **title compound**: (2.2 g, 82%). δ_H (d_6-DMSO) 1.30 (t, *J*=7.0 Hz, 3H), 4.33 (q, *J*=7.0 Hz, 2H), 7.56 (m, 2H), 7.68 (m, 2H), 8.00 (m, 2H), 8.43 (m, 1H), 8.58 (m, 1H), 11.82 (br, 1H), 12.96 (br, 1H).

b) Potassium 1*H*-pyrido[3,2-*d*]pyrimidin-4-one-2-thiolate. 3-(3-Benzoylthioureido)pyridine-2-carboxylic acid ethyl ester (2.2 g) was treated in the same way as for **Intermediate 3a** to yield the crude **title compound** which was used directly in the next step without further purification: (1.6 g) *m/z* (APCI) 180 ($M+H^+$, 95%), 440 (100%).

c) 2-Methylsulfanyl-1*H*-pyrido[3,2-*d*]pyrimidin-4-one. Crude potassium 1*H*-pyrido[3,2-*d*]pyrimidin-4-one-2-thiolate (1.6 g) was treated in the same way as for **Intermediate 3b** to yield the **title compound**: (458 mg, 36% over steps **(b)** and **(c)**), *m/z* (APCI) 194 ($M+H^+$, 100%).

d) 2-(3-Aminopropylamino)-1*H*-pyrido[3,2-*d*]pyrimidin-4-one. 2-Methylsulfanyl-1*H*-pyrido[3,2-*d*]pyrimidin-4-one (450 mg) was treated in the same way as for **Intermediate 2** to yield the **title compound**: (100 mg, 19%) *m/z* (ESI) 218 ($[M-H]^-$, 100%).

e) 2-[3-(3,5-Dibromo-2-ethoxybenzylamino)prop-1-ylamino]-1*H*-pyrido[3,2-*d*]pyrimidin-4-one dihydrochloride. According to the **general method for reductive amination**, 2-(3-aminopropylamino)-1*H*-pyrido[3,2-*d*]pyrimidin-4-one (90 mg) was allowed to react with 3,5-dibromo-2-ethoxybenzaldehyde (126 mg) to yield the **title compound** as an off-white solid: (81 mg, 39%), *m/z* (ESI) 512 ($M+H^+$, 32%), 203 (100%).

Example 14 - 2-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-1*H*-pyrimido[4,5-*d*]pyrimidin-4-one

Example 5 (334 mg) was heated with 2-methylsulfanyl-1*H*-pyrimido[4,5-*d*]pyrimidin-4-one (100 mg) for 18 h at 85 °C. The reaction mixture was purified by column chromatography to yield the **title compound** as a pale yellow solid: (10 mg, 4%), *m/z* (ESI) 469 ($M+H^+$, 100%).

Example 15 - 2-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-1*H*-thieno[2,3-*d*]pyrimidin-4-one dihydrochloride

a) 2-(3-Benzoylthioureido)thiophene-3-carboxylic acid methyl ester. 2-Aminothiophene-3-carboxylic acid methyl ester (2.4 g; Gewald, *Chem. Ber.* **1965**, *98*, 3571-3577) was treated as for **13a** to yield the **title compound** as an off-white solid: (3.6 g, 74%) *m/z* 319 ($M+H^+$, 100%).

b) Potassium 1*H*-thieno[2,3-*d*]pyrimidin-4-one-2-thiolate. 2-(3-Benzoylthioureido)thiophene-3-carboxylic acid methyl ester (2.9 g) was treated in the same way as for **intermediate 3a** to yield the crude **title compound**: (1.2 g), δ_H (d_4-MeOH) 6.36 (m, 1H), 6.58 (m, 1H); contains 1:1 benzoate:desired product; used crude in next step.

c) 2-Methylsulfanyl-1*H*-thieno[2,3-*d*]pyrimidin-4-one. The crude material from step **b)** was treated in the same way as for **intermediate 3b** to yield the crude **title compound** as an off-white solid which was used without further purification: (906 mg), *m/z* (APCI) 199 ($M+H^+$, 100%).

d) 2-[3-(3,5-Dibromobenzylamino)prop-1-ylamino]-1*H*-thieno[2,3-*d*]pyrimidin-4-one dihydrochloride. Example 5a (190 mg) was heated with 2-methylsulfanyl-1*H*-thieno[2,3-*d*]pyrimidin-4-one (60 mg) for 26 h at 125 °C. The reaction mixture was purified by column chromatography and the product

converted to the corresponding dihydrochloride salt using conc. HCl in methanol to yield the **title compound** as an off-white solid: (50 mg, 31%), *m/z* (ESI) 473 ($M+H^+$, 100%).

Example 16 - 2-[3-(3,5-Dichloro-2-ethoxybenzylamino)prop-1-ylamino]-1*H*-quinazolin-4-one dihydrochloride

a) 3,5-Dichloro-2-ethoxybenzaldehyde 3,5-Dichloro-2-hydroxybenzaldehyde was alkylated on a 5.2 mmol scale using the **general method for alkylation of phenols** to give the **title compound** as a yellow solid (1.14 g, 99%); *m/z* (ES^+) 219 (MH^+, 70%).

b) 2-[3-(3,5-Dichloro-2-ethoxybenzylamino)prop-1-ylamino]-1*H*-quinazolin-4-one dihydrochloride According to the **general method for reductive amination**, 3,5-dichloro-2-ethoxybenzaldehyde (44 mg) was allowed to react with **intermediate 2** (44 mg) to yield the **title compound** as an off-white solid: (29 mg, 29%), *m/z* (ESI) 421 ($M+H^+$, 9%), 202 (100%).

Example 17 - 2-[3-(3,5-Dibromo-2-ethoxybenzylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one dihydrochloride

According to the **general method for reductive amination**, 3,5-dibromo-2-ethoxybenzaldehyde (92 mg) was allowed to react with **intermediate 3** (89 mg) to yield the **title compound** as an off-white solid: (58 mg, 33%), *m/z* (ESI) 208 (100%), 517 ($M+H^+$, 25%).

Example 18 - 2-[3-(6-Chloro-8-iodochroman-4-ylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one dihydrochloride

6-Chloro-8-iodochroman-4-one (300 mg) and **intermediate 3** (289 mg) were dissolved in 3% v/v acetic acid in methanol (10 ml) and sodium methoxide (104 mg) added. Sodium cyanoborohydride (122 mg) was added and the reaction mixture heated for 24 h at 80 °C. The mixture was evaporated *in vacuo* and the residue purified by column chromatography. The product was converted to the corresponding dihydrochloride salt using conc. HCl in methanol to yield the **title compound** as an off-white solid: (20 mg, 4%), *m/z* (ESI) 517 ($M+H^+$, 100%).

Example 19 - 2-[3-(6,8-Dibromochroman-4-ylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one dihydrochloride - According to the procedure used for **example SA6**, 6,8-dibromochroman-4-one **(ref WO 00/, SmithKine Beecham)** (92 mg) was allowed to react with **intermediate 3 dihydrochloride** (89 mg) to yield the **title compound** as a white solid: (9 mg, 5%), *m/z* (ESI) 515 ($M+H^+$, 25%).

Example 20 - 2-[3-(6-Bromo-8-chloro-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-quinazolin-4-one dihydrochloride
6-Bromo-8-chloro-2,3-dihydro-1*H*-quinolin-4-one **(ref WO 00/, SmithKine Beecham)** (40 mg) and **intermediate 2 dihydrochloride** (45 mg) were dissolved in 3% v/v acetic acid in methanol (5 ml). Sodium cyanoborohydride (50 mg in total) was added and the reaction mixture heated to 85°C for a total of 76 h. The reaction mixture was passed down a cation exchange cartridge and the residue purified by column chromatography. The product was converted to the corresponding dihydrochloride salt using conc. HCl in methanol to yield the **title compound** as an off-white solid: (4 mg, 4%), *m/z* (ESI) 462 ([M-H]$^-$, 100%).

Example 21 - 2-[3-(6-Ethyl-8-iodo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-quinazolin-4-one dihydrochloride
According to the procedure used for **example 20**, 6-ethyl-8-iodo-2,3-dihydro-1*H*-quinolin-4-one **(ref WO 00/, SmithKine Beecham)** (60 mg) was allowed to react with **intermediate 2 dihydrochloride** (58 mg) to yield the **title compound** as an off-white solid: (10 mg, 8%), *m/z* (ESI) 504 (M+H$^+$, 15%), 286 (100%).

Example 22 - 2-[3-(6,8-Dibromo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]- 1*H*-thieno[3,2-*d*]pyrimidin-4-one dihydrochloride
According to the procedure used for **example 18**, 6,8-dibromo-2,3-dihydro-1*H*-quinolin-4-one (304 mg) was allowed to react with **intermediate 3 dihydrochloride** (149 mg) to yield the **title compound** as an off-white solid: (13 mg, 4%), *m/z* (ESI) 514 (M+H$^+$, 100%).

Example 23 - 2-[3-(6,8-Dibromo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-quinazolin-4-one dihydrochloride
According to the procedure used for **example 20**, 6,8-dibromo-2,3-dihydro-1*H*-quinolin-4-one (52 mg) was allowed to react with **intermediate 2 dihydrochloride** (58 mg) to yield the **title compound** as an off-white solid: (1 mg, 1%), *m/z* (ESI) 508 (M+H$^+$, 100%).

Example 24 - 2-[3-(6-Bromo-8-methoxy-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-quinazolin-4-one
a) 3-(2-Methoxy-4-bromophenylamino)propionic acid 3-(2-Methoxyphenylamino)propionic acid (*J. Chem. Soc., Perkin 1,* **1972,** 932; *J. Med. Chem.,* **1965,** *8,* 566;1.95 g, 10 mmol) dissolved in dry DMF (20 ml) at 0°C was treated with recrystallised N-bromosuccimide (1.78 g, 10 mmol). After stirring for 4 h at room temperature the DMF was evaporated and the residue partitioned between diethyl ether (50 ml) and water (50 ml). The organic layer was separated, washed with water, dried and evaporated to yield the **title**

compound as a brown solid; δ ($CDCl_3$ + D_2O) 2.68 (2H, t, J = 6.4 Hz), 3.46 (2H, t, J = 6.8 Hz), 3.82 (3H, s), 6.48 (1H, d, J = 8.4 Hz), 6.85 (1H, d, J = 2 Hz), 6.97 (1H, d x d, J = 2 & 8.4 Hz); MS AP^- 272^{Br79} (100%) MH^-.

b) 6-Bromo-8-methoxy-2,3-dihydro-1*H*-quinolin-4-one 3-(2-methoxy-4-bromophenylamino)propionic acid (1 g, 3.65 mmol) was added to a mixture of phosphorus pentoxide (35 g) in 85 % phosphoric acid (15 ml) at 100°C. After 1 h the resultant deep red mixture was poured onto ice and the aqueous solution made alkaline by cautious treatment with concentrated ammonium hydroxide. The organic material was extracted with ethyl acetate (3 x 50 ml) and the combined organic phases were washed with saturated sodium carbonate solution. The organic phase was separated, dried and evaporated to yield the **title compound** as a bright yellow solid; δ ($CDCl_3$) 2.70 (2H, t, J = 6.8 Hz), 3.60 (2H, d x t, J = 2.4 & 7.1 Hz), 3.87 (3H, s), 4.92 (1H, brd. s), 6.90 (1H, d, J = 2 Hz), 7.59 (1H, d, J = 2 Hz); MS AP^+ 256^{Br79} (100%) MH^+

c) 2-[3-(6-Bromo-8-methoxy-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-quinazolin-4-one A mixture of 6-bromo-8-methoxy-2,3-dihydro-1*H*-quinolin-4-one, (85 mg, 0.33 mmol), **intermediate 2 dihydrochloride** (58 mg, 0.2 mmol) and sodium acetate (32.8 mg, 0.4 mmol) in 3% acetic acid in methanol (5 ml) was heated at reflux for 1h, cooled, and sodium cyanoborohydride (20 mg, 0.32 mmol) added. After a further 48 h reflux the mixture was cooled and the solvent evaporated. The crude product was chromatographed over silica gel eluting with dichloromethane-methanol-ammonium hydroxide mixtures to yield the free base. Treatment with 1M methanolic hydrogen chloride gave the **title compound** as a cream solid; δ (CD_3OD) 1.78-1.93 (2H, m), 2.82 (2H, t, J = 6.84 Hz), 3.21-3.43 (6H, m), 3.75 (3H, s), 3.54-3.55 (1H, m), 6.76 (1H, d, J = 2 Hz), 6.92 (1H, d, J = 1.6 Hz), 7.18 (1H, J = 7.12 Hz), 7.23 (1H, d, J = 8.32 Hz), 7.59 (1H, t, J = 7.0 Hz), 7.98 (1H, d, J = 8.1 Hz); MS ES^- 456^{Br79} (100%) $[M-H]^-$.

Example 25 - 2-[3-(4,5-Dibromo-3-methylthien-2-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,4-*d*]pyrimidin-4-one dihydrochloride

a) 2-Methylsulfanyl-1*H*-thieno[3,4-*d*]pyrimidin-4-one. 4-Aminothiophene-3-carboxylic acid methyl ester was liberated from the hydrochloride salt by passing down a column of alumina eluting with 10% methanol in dichloromethane. The free amine (4 g) was treated in the same way as for **example 13a – 13c** to yield the **title compound** (520 mg, 10% over 3 steps): δH (d_6-DMSO) 2.49 (br, 3H), 7.60 (m, 1H), 8.40 (m, 1H), 12.0 (br, 1H).

b) 2-(3-Aminopropylamino)-1*H*-thieno[3,4-*d*]pyrimidin-4-one. 2-Methylsulfanyl-1*H*-thieno[3,4-*d*]pyrimidin-4-one (310 mg) was suspended in dioxane at 0 °C and hydrogen peroxide solution (3% w/w in H_2O, 3.5 ml) added, followed by acetic acid (5 drops) and a catalytic amount of methyl trioxorhenium.

After stirring for 90 minutes at 25 °C the yellow solution was treated with MnO_2, filtered through Celite and evaporated *in vacuo*. The crude product was heated with 1,3-diaminopropane (0.63 ml) for 18 h at 80 °C and purified by column chromatography to yield fractions containing the **title compound** which were used without further purification (100 mg), *m/z* (APCI) 225 ($M+H^+$, 35%), 208 (100%).

c) 5-Bromo-3-methylthiophene-2-carboxaldehyde 3-Methylthiophene-2-carboxaldehyde (5 g, 39.6 mmol) was dissolved in dry chloroform (100 ml) and the solution cooled to 0°C. Bromine (6.33 g, 39.6 mmol) was added dropwise then the reaction stirred at room temperature for 16 hours. The solution was diluted with chloroform, washed with 1M aqueous sodium carbonate and water. The organic solution was dried and evaporated. The residue was chromatographed on Kieselgel 60 eluting with 1:1 dichloromethane-hexane. Product-containing fractions were combined and evaporated to afford the **title compound** as a yellow solid (7.5 g, 92%); δ_H ($CDCl_3$) 2.53 (3H, s, CH_3), 6.96 (1H, s, Ar-H), 9.9 (1H, s, CHO).

d) 4,5-Dibromo-3-methylthiophene-2-carboxaldehyde 5-Bromo-3-methylthiophene-2-carboxaldehyde (7.5 g, 36.5 mmol) was dissolved in dry chloroform (75 ml), aluminium trichloride (12.2 g, 91.42 mmol) was added and the reaction mixture stirred for five minutes before the addition of bromine (5.84 g, 36.5 mmol). The reaction was stirred at room temperature for 16 hours, diluted with chloroform, and washed with aqueous sodium bicarbonate and water. The organic solution was dried and evaporated. The residue was chromatographed on Kieselgel 60 eluting with dichloromethane. Product-containing fractions were combined and evaporated to afford the **title compound** as a pale yellow solid (7.02 g, 70%); δ_H ($CDCl_3$) 1.53 (3H, s, CH_3), 9.93 (1H, s, CHO).

e) 2-[3-(4,5-Dibromo-3-methylthien-2-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,4-*d*]pyrimidin-4-one dihydrochloride. According to the **general method for reductive amination,** 4,5-dibromo-3-methylthiophene-2-carbaldehyde (70 mg) was allowed to react with the product of **b)** (50 mg) to yield the **title compound** as an off-white solid: (20 mg, 16%) *m/z* (ESI) 492 ($M+H^+$, 100%).

Example 26 - 2-[3-(4,5-Dibromothien-2-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one dihydrochloride

According to the **general method for reductive amination,** 4,5-dibromothien-2-carbaldehyde (54 mg, 0.2 mmol) was allowed to react with **intermediate 2** (43mg, 0.2mmol) to yield the **title compound** as a white solid: (29mg, 26%). MS (ES^+) 471/473/475 (12/24/13%) MH^+, 253/255/257 (50/100/50%).

Example 27 - 2-[3-(4,5-Dibromothien-2-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-d]pyrimidin-4-one dihydrochloride
According to the **general method for reductive amination,** 3,4-dibromothiophene-2-carbaldehyde (54 mg, 0.2 mmol) was allowed to react with **intermediate 3** (45 mg, 0.2 mmol) to yield the **title compound** as a white solid: (17 mg); MS ES^+ 478(27%)MH^+.

Example 28 - 2-[3-(4,6-Dichloro-1*H*-indol-2-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one dihydrochloride
According to the **general method for reductive amination,** 4,6-dichloro-1*H*-indole-2-carbaldehyde (WO 99/55677; 150 mg) was allowed to react with **intermediate 2** (153 mg) to yield the **title compound** as an off-white solid: (130 mg, 38%) *m/z* (ESI) 416 ($M+H^+$, 100%).

Example 29 - 2-[3-(4,6-Dichloro-1*H*-indol-2-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one dihydrochloride
According to the **general method for reductive amination**, 3,4-dichloro-1*H*-indole-2-carbaldehyde (WO 99/55677; 150 mg) was allowed to react with **intermediate 3 dihydrochloride** (208 mg) to yield the **title compound** as a white solid: (65 mg, 19%) *m/z* (ESI) 422 ($M+H^+$, 100%).

Example 30 - 2-{3-[3,5-Dibromo-2-(3-morpholinopropoxy)benzylamino]-prop-1-ylamino}-1*H*-quinazolin-4-one trihydrochloride
a) 3,5-Dibromo-2-(3-morpholinopropoxy)benzaldehyde
A mixture of 3,5-dibromo-2-hydroxybenzaldehyde (2.80 g), *N*-(3-chloropropyl)morpholine hydrochloride (2.00 g; Schliemann, W.; Buege, A.; Reppel, L. *Pharmazie* **1980**, *35*, 69-72), tetra-*n*-butylammonium iodide (0.74 g), potassium carbonate (1.52 g), and *N,N*-dimethylformamide (15 ml) were stirred at room temperature for 1 h and at 60 °C for 16 h. The mixture was then partitioned between water and ethyl acetate. The organic layer was washed (aq. $NaHCO_3$, brine) and concentrated to give the **title compound** as an orange oil in sufficient purity for the next step: (4.76 g), *m/z* (ESI) 406 (MH^+, 32%).
b) 2-{3-[3,5-Dibromo-2-(3-morpholinopropoxy)benzylamino]prop-1-ylamino}-1*H*-quinazolin-4-one trihydrochloride - According to the **general method for reductive amination** 3,5-dibromo-2-(3-morpholinopropoxy)benzaldehyde (105 mg) was allowed to react with **intermediate 2** (44 mg). The product was isolated by column chromatography, treated with excess HCl in methanol, the volatiles evaporated, and the residue dissolved in water and lyophylised to give the **title compound** (88 mg) as a colourless solid: *m/z* (ESI) 610 (MH^+, 76%).

Example 31 - 2-{3-[3,5-Dibromo-2-(3-morpholinopropoxy)benzylamino]-prop-1-ylamino}-1*H*-thieno[3,2-*d*]pyrimidin-4-one trihydrochloride According to the **general method for reductive amination example 30a** (105 mg) was allowed to react with **intermediate 3** (45 mg). The product was isolated by column chromatography, treated with excess HCl in methanol, the volatiles evaporated, and the residue dissolved in water and lyophylised to give the **title compound** (74 mg) as a colourless solid: *m/z* (ESI) 616 (MH^+, 57%).

Example 32 - 2-{3-[4,6-Dichloro-1-(2-hydroxyethyl)-1*H*-indol-2-ylmethylamino]prop-1-ylamino}-1*H*-thieno[3,2-d]pyrimidin-4-one

a) 4,6-Dichloro-1-(methoxycarbonylmethyl)-1*H*-indole-2-carboxylic acid ethyl ester 4,6-Dichloro-1*H*-indole-2-carboxylic acid ethyl ester (0.516 g, 2 mmol) was disolved in DMF (5 ml) and then potassium carbonate (0.276 g, 2 mmol) was added. The mixture was stirred under argon for 30 min, then methyl bromoacetate (0.19 ml, 2 mmol) added. The mixture was stirred for a further 2.5 h, then diluted with water and extracted with diethyl ether. The combined organic extracts were washed with brine, dried and evaporated to give the **title compound** as a beige powder (0.65 g, 98%); MS (APCI +ve) 330, 332 (30, 21%, MH^+).

b) 2-(4,6-Dichloro-2-hydroxymethyl-1*H*-indol-1-yl)ethanol 4,6-Dichloro-1-(methoxycarbonylmethyl)-1*H*-indole-2-carboxylic acid ethyl ester (0.625 g, 1.89 mmol) was dissolved in THF (20 ml), cooled in an ice/salt bath under argon, and treated slowly with a solution of lithium aluminium hydride (1M in THF, 2.27 ml, 2.27 mmol). The mixture was stirred for 2 h then quenched carefully with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and evaporated to give the crude product as an oily solid (0.5 g, q). This material was used without further purification.

c) 4,6-Dichloro-1-(2-hydroxyethyl)-1*H*-indole-2-carbaldehyde The crude material (max 1.89 mmol) from **b)** above was dissolved in dichloromethane (50 ml), manganese dioxide (1.64 g, 18.9 mmol) was added, and the mixture stirred for 3.5 h. The mixture was filtered, washing well with dichloromethane and 1,4-dioxane, then evaporated to give a solid. This material was dissolved in dichloromethane, pre-absorbed onto silica, then purified by flash chromatography, eluting with 0 – 20% ethyl acetate in 40 – 60 pet ether, to give the **title compound** as a white powder (0.203 g, 39%); MS (APCI –ve) 257, 259 (100, 66%, $M-H^-$).

d) 2-{3-[4,6-Dichloro-1-(2-hydroxyethyl)-1*H*-indol-2-ylmethylamino]prop-1-ylamino}-1*H*-thieno[3,2-d]pyrimidin-4-one According to the **general method for reductive amination** the product of **c)** was allowed to react with **intermediate 3** to give the **title compound** as a white powder (0.03 g, 32%); LC/MS (ES+) 466, 468 (15, 10%, MH^+).

Example 33 - 2-[3-(2-Ethoxy-5-iodo-3-methylbenzylamino)prop-1-ylamino]-1*H*-quinazolin-4-one

a) 2-Hydroxy-5-iodo-3-methylbenzaldehyde 2-Hydroxy-3-methylbenzaldehyde (272 mg, 2.0 mmol) was dissolved in dimethylformamide (10 ml), treated with sodium iodide (360 mg, 2.4 mmol) then chloramine T (546 mg, 2.4 mmol). After stirring at room temperature for 4 h, the suspension was treated with water, acidified with 1N HCl and the mixture extracted with ethyl acetate. The organic layer was washed successively with a 5% aqueous solution of sodium thiosulphate, brine then dried and evaporated. The residue was chromatographed on Kieselgel 60 eluting with 0-50% toluene in hexane. Product-containing fractions were combined and evaporated to give the **title compound** as a white solid (330 mg, 63%); *m/z* (AP^-) 261 ($[M-H]^-$, 20%).

b) 2-Ethoxy-5-iodo-3-methybenzaldehyde 2-Hydroxy-5-iodo-3-methylbenzaldehyde was alkylated on a 1.2 mmol scale using the **general method for alkylation of phenols** to give the **title compound** as a white solid (350 mg, 100%); δ_H ($CDCl_3$) 1.43 (3H, t, J =7.0 Hz, CH_3), 2.29 (3H, s, CH_3), 3.99 (2H, q, J =7.0 Hz, OCH_2), 7.74 (1H, d, J =2.3 Hz, Ar-H), 7.96 (1H, d, J=2.3 Hz, Ar-H), 10.25 (1H, s, CHO).

c) 2-[3-(2-Ethoxy-5-iodo-3-methylbenzylamino)prop-1-ylamino]-1*H*-quinazolin-4-one 2-Ethoxy-5-iodo-3-methybenzaldehyde was coupled to **intermediate 2** on a 0.2 mmol scale using the **general method for reductive amination** to give the **title compound** as a white solid (66 mg, 67%); *m/z* (ES^+) 493 (MH^+, 100%)

Example 34 - 5-[3-(3,4-Dichlorobenzylamino)prop-1-ylamino]-4*H*-thieno[3,4-*b*]pyridin-7-one dihydrochloride

a) 2-[3-(3,4-Dichlorobenzylamino)prop-1-ylamino]-4-methoxythieno[3,4-*b*]pyridine 2-Chloro-4-methoxythieno[3,4-*b*]pyridine (0.13 g; Barker *et al*, *J. Chem. Res. Miniprint* **1989**, *7*, 1501-1523) and **intermediate 1** (0.4 ml) were heated with stirring at 120 °C for 16 h. The product was purified by column chromatography eluting with 6-10% [10:1 MeOH/conc. NH_3(aq.)] in CH_2Cl_2 to yield the **title compound** (40 mg) as a brown oil: *m/z* (ESI) 419 ($M+Na^+$, 20%).

b) 5-[3-(3,4-Dichlorobenzylamino)prop-1-ylamino]-4*H*-thieno[3,4-*b*]pyridin-7-one dihydrochloride 2-[3-(3,4-Dichlorobenzylamino)prop-1-ylamino]-4-methoxythieno[3,4-*b*]pyridine (40 mg) was heated in an oil bath of 120°C in dioxane (0.5 ml) and concentrated aqueous HCl (5 ml) for 16 h. Dioxane (2 ml) was added and heating continued for 7 h. The volatiles were then evaporated and the residue was triturated with chloroform, the solid collected by filtration, and further purified by column chromatography eluting with 10 - 25% [10:1

MeOH/conc. NH_3(aq.)] in CH_2Cl_2. The oil thus obtained was treated with excess HCl in methanol, the volatiles were evaporated, and the residue was triturated with chloroform to yield, after filtration, the **title compound** (18 mg) as an off-white solid: *m/z* (ESI) 404 ($M+Na^+$, 13%); 382 ($M+H^+$, 20%).

Biological Data

1. Enzyme Inhibition – aminoacylation assay

Compounds of the present invention may be assayed for their ability to inhibit the enzyme methionyl tRNA synthetase (MRS), using recombinant *S. aureus* MRS, as follows:

Reaction Mix (per 1ml)

Stock	Volume (ul)	Final Concentration
100mM Tris/Cl, pH 7.9	600	30 mM
250 mM KCl		75 mM
125 mM ATP	40	2.5 mM
250 mM $MgCl_2$	80	10 mM
50 mM DTT	80	2 mM
0.5mM Met (S-35 hot and cold)	40	10 uM
Solid tRNA (Mixed E. coli MRE 600)	4mg/ml	2mg/ml
H_2O	160	
10 x Inhibitor (0 - 100 uM)	5 ul per well	0 - 10 uM

The reaction is started by adding 20 ul appropriately diluted pure enzyme (pre-incubated with inhibitor) to 25 ul reaction mix for 10 min at room temperature. The reaction is terminated by the addition of 100 ul 5% trichloroacetic acid, 10% glycerol. The TCA precipitate is harvested onto dry Unifilter GFC plates using a Packard Filtermate Cell Harvester. The filters are washed with 4 x 200ul of 50% industrial methylated spirit, before drying. 30 ul of Microscint 20 is added to each well and plates are counted on a TopCount. (Packard 96 well counter).

Reagents

Mixed E. coli MRE 600 tRNA and ATP were purchased from Boehringer-Mannheim, L-[^{35} S] methionine from Amersham and other reagents from Sigma.

Pure recombinant *S. aureus* MRS (EP application number 97300317.1, SmithKline Beecham) was obtained using standard purification procedures. The enzyme is diluted in Dilution Buffer which consists of 10 mM Tris / Cl, 2 mM DTT pH 7.9.

Results

Examples 1 to 34 have IC_{50} values against *S. aureus* MRS in the range <3 to 800 nM. All are highly selective with respect to the mammalian enzyme (no inhibition of rat MRS up to 1 uM).

2. Antibacterial Activity

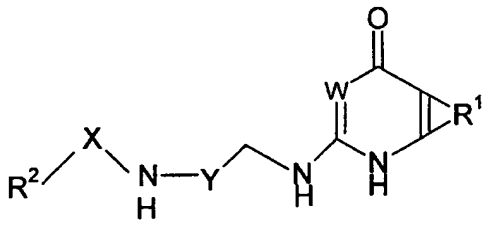
Compounds of the present invention were assayed for antibacterial activity against a range of pathogenic organisms (strains of *S aureus*, *S pneumoniae*, *E faecalis*, *H influenzae* and *M catarrhalis*) in a standard MIC assay modified by the inclusion of cyclodextrin, to assist with solubility.

Examples 1, 3, 5, 6, 8-12, 16-25, and 27-33 had MIC's < 1μg/ml against some strains of the organisms *S. aureus*, *S. pneumoniae*, and *E. faecalis*; and MIC's against *M. Catarrhalis*, in the range 2 - >64 μg/ml.

Examples 28 and 29 were active against *H. influenzae*.

Claims

1. A compound of formula (I):



(I)

in which:

W is CH and R1 is the residue of a 5 or 6-membered heteroaryl ring, or W is N and R1 is the residue of an 5 or 6-membered heteroaryl ring or an aryl ring, which heteroaryl or aryl ring is optionally substituted with from 1 to 3 substituents selected from halo, cyano, hydroxy, (C1-6)alkyl (optionally substituted by halo, hydroxy, amino, mono to perfluoro(C1-3)alkyl, carboxy or (C1-6)alkoxycarbonyl), (C3-7)cycloalkyl, C(1-6)alkoxy, amino, mono- or di-(C1-6)alkylamino, acylamino, carboxy, (C1-6)alkoxycarbonyl, carboxy(C1-6)alkyloxy, (C1-6)alkylthio, (C1-6)alkylsulphinyl, (C1-6)alkylsulphonyl, sulphamoyl, mono- and di-(C1-6)alkylsulphamoyl, carbamoyl, mono- and di-(C1-6)alkylcarbamoyl, and heterocyclyl;

R2 is an optionally substituted aryl or an optionally substituted heteroaryl ring;X is CH2 or CHR3 in which R3 is C(1-6)alkyl or R3 may be linked to the ortho position of an aryl or heteroaryl ring of R2 to form a 5 to 7 membered ring optionally including oxygen or nitrogen as a ring atom;

Y is C(1-3)alkylene or C(4-6)cycloalkylene;

including tautomeric forms of the pyrimidone ring (when W is N); and salts thereof, preferably pharmaceutically acceptable salts thereof.

2. A compound of formula (I) as claimed in claim 1 in which R^1 is the residue of a ring in which the heteroatom is sulphur, for instance thieno, or nitrogen, for instance pyrido and pyrazolo.

3. A compound of formula (I) as claimed in claim 1 or 2 in which R^1 is the residue of a ring which is selected from thieno, pyrido and pyrazolo.

4. A compound of formula (I) as claimed any one of claims 1 to 3 in which X is CH_2 or forms with R^2 a 5-7-membered ring fused to an aryl ring or a heteroaryl ring which includes oxygen or nitrogen as a ring atom.

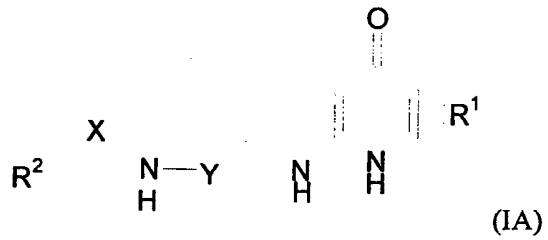
5. A compound of formula (I) as claimed any one of claims 1 to 4 in which R^2 when aryl is selected from phenyl and naphthyl, each of which may be optionally substituted with up to four substituents; or when heteroaryl is selected from pyrrolyl, thienyl, furanyl, pyridyl, quinolinyl, benzofuranyl, and indolyl, each of which may be optionally substituted with up to three substituents.

6. A compound of formula (I) as claimed in claim 5 in which aryl and heteroaryl groups for R^2 are phenyl and indolyl, respectively.

7. A compound of formula (I) as claimed any one of claims 1 to 4 in which R^2X is benzyl, chroman-4-yl, 1,2,3,4-tetrahydroquinolin-4-yl, indol-2-ylmethyl, and thien-2-ylmethyl in which the aryl/heteroaryl ring may be optionally substituted.

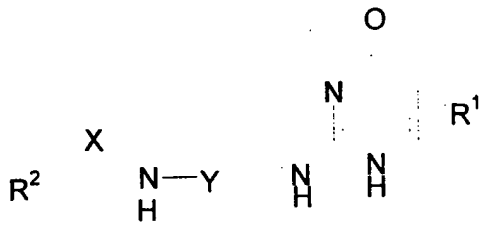
8. A compound of formula (I) as claimed any one of claims 1 to 7 in which Y is a C_2 alkylene chain.

9. A compound as claimed in any one of claims 1 to 8 of the formula (IA) or (IB):



(IA)

and a second set of pyrimidone compounds in which W is N:



(IB).

10. A compound of formula (I) as claimed in claim 1 selected from any one of the compounds named in the main title of Examples 1 to 34.

11. A compound of formula (I) as claimed in claim 10 selected from:
2-[3-(3-Bromo-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one;
2 -[3-(3-Bromo-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;
2-[3-(3-Chloro-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one;
2 -[3-(3-Chloro-5-methoxy-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;
2 -[3 -(3-Chloro-5-methyl-1*H*-indol-7-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;
2-[3-(6-Chloro-8-iodochroman-4-ylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;
2-[3-(6,8-Dibromochroman-4-ylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;
2-[3-(6-Bromo-8-chloro-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-quinazolin-4-one;
2-[3-(6,8-Dibromo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]- 1*H*-thieno[3,2-*d*]pyrimidin-4-one;
2-[3-(6,8-Dibromo-1,2,3,4-tetrahydroquinolin-4-ylamino)prop-1-ylamino]-1*H*-quinazolin-4-one;
2-[3-(4,6-Dichloro-1*H*-indol-2-ylmethylamino)prop-1-ylamino]-1*H*-quinazolin-4-one;
2-[3-(4,6-Dichloro-1*H*-indol-2-ylmethylamino)prop-1-ylamino]-1*H*-thieno[3,2-*d*]pyrimidin-4-one;

2-{3-[3,5-Dibromo-2-(3-morpholinopropoxy)benzylamino]-prop-1-ylamino}-1*H*-quinazolin-4-one;

2-{3-[4,6-Dichloro-1-(2-hydroxyethyl)-1*H*-indol-2-ylmethylamino]prop-1-ylamino}-1*H*-thieno[3,2-d]pyrimidin-4-one; and

2-[3-(2-Ethoxy-5-iodo-3-methylbenzylamino)prop-1-ylamino]-1*H*-quinazolin-4-one.

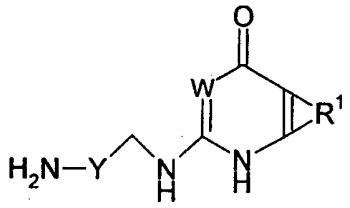
12. A pharmaceutical composition comprising an antibacterially effective amount of a substance or compound of formula (I) as claimed in claim 1 together with a pharmaceutically acceptable carrier or excipient.

13. A compound of formula (I) as claimed in for use in therapy.

14. A compound of formula (I) as claimed in for use in the treatment of bacterial infections.

15 Use of a compound of formula (I) as claimed in claim 1 in the manufacture of a medicament for use in the treatment of bacterial infections.

16. A process for preparing a compound of formula (I) as claimed in claim 1 which process comprises reacting a compound of formula (II):



(II)

in which R^1, W and Y are as hereinbefore defined;

with either:

(a) for a compound of formula (I) in which X is CH_2, an aldehyde of formula (III):

$$R^2CHO \qquad \text{(III)}$$

in which R^2 is as hereinbefore defined,

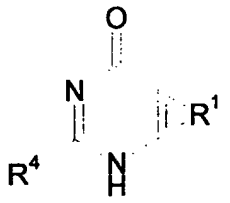
under reductive alkylation conditions;

(b) for a compound of formula (I) in which X is CH_2 substituted by $C_{(1-6)}$ alkyl or in which R^2 and X are linked by a 5-7-membered ring opt.cont. oxygen or nitrogen, a ketone of formula (IV):

$$R^2R^3CO \qquad (IV)$$

in which R^2 and R^3 are as hereinbefore defined,
under reductive alkylation conditions;

(c) for a compound of formula (IB), reacting a compound of formula (V):



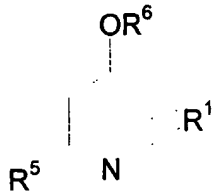
(V)

in which R^1 is as hereinbefore defined; and
R^4 is a leaving group such as halo, for instance chloro, or $C_{(1-6)}$ alkylthio;
with an amine of the formula (VI):

$$R^2XNHYCH_2NH_2 \qquad (VI)$$

in which R^2, X and Y are as hereinbefore defined;
or an activated derivative thereof;
under nucleophilic displacement conditions; or

(d) for a compound of formula (IA), reacting a compound of formula (VII):



(VII)

in which R^1 is as hereinbefore defined;

R^5 is a leaving group such as halo, for instance chloro; and

R^6 is a $C_{(1-6)}$ alkyl, for instance methyl or ethyl, or an aryl$C_{(1-4)}$ alkyl group;

with an amine of the formula (VI), as hereinbefore defined;

or an activated derivative thereof;

under nucleophilic displacement conditions; to form an intermediate which is then converted into a compound of formula (IA) by acidic hydrolysis.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/04436

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/90 C07D239/88 C07D403/12 C07D495/04 C07D401/12
C07D405/12 C07D487/04 C07D471/04 A61K31/4365 A61K31/517
A61K31/519 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 00 21949 A (JARVEST RICHARD LEWIS ;BERGE JOHN MICHAEL (GB); ELDER JOHN STEPHEN) 20 April 2000 (2000-04-20) cited in the application the whole document	1,12-15
X,P	WO 99 55677 A (HAMPRECHT DIETER WOLFGANG ;JARVEST RICHARD LEWIS (GB); MCNAIR DAVI) 4 November 1999 (1999-11-04) cited in the application the whole document	1,12-15
A	US 5 827 857 A (RIEDL BERND ET AL) 27 October 1998 (1998-10-27) the whole document	1,12-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 October 2000	02/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bosma, P

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/04436

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